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929,391

PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Therapeutic Compositions comprising Polymeric Amines

We, MERCK & CO., INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to methods and compositions for lowering the blood level of cholesterol.

Heart disease has been the leading cause of death in the United States in recent years. Atherosclerosis is one of the most significant forms of cardiovacular disease because of its frequent occurrence and its predilection for serious ailments such as coronary thrombosis. Atherosclerosis is characterised by thickening of intima, reduction in diameter, and loss of elasticity of arterics, due to fatty accumulations. Higher blood levels of cholesterol are observed in atherosclerosis patients than in normal persons. Accordingly, it is considered important in the treatment and prevention of atherosclerosis to maintain normal blood cholesterol levels.

The common atherosclerosis therapy up to the present time has been a low fat diet, devoid as far as possible of animal fats. This necessitates reduced consumption of nutritious foods such as meat, milk, and eggs. It is evident that a more desirable therapy would be to permit the patient to have a normal diet and to maintain the cholesterol blood level where desired by control with a therapeutic agent. However, prior to the present invention no therapeutic agents for maintaining desired blood levels of cholesterol which are both safe and effective have been found.

It has now been found that blood levels of cholesterol can be maintained at a desired level by the oral administration of certain non-toxic glycocholic acid-binding polymeric amines.

In accordance with the present invention, an orally administerable pharmaceutical composition for binding bile acids in the gastrointestinal tract into a non-absorbable form comprises a synthetic non-toxic polymer having a polymeric skeleton inert to digestive enzymes and a molecular weight in excess of about 3,000 and containing ionizable amino groups as herein defined, the polymer, if water-insoluble, having the property of binding at least 30% of the available glycocholic acid into a form incapable of dialysis through a cellulose membrane within 5 minutes when exposed to an aqueous solution of an equal weight of said acid and having a moisture content greater than 65% after equilibration with air at 100% relative humidity at 25°C, and, if water-soluble, having an equivalent weight, based on the ionizable amino groups, of less than 500 and the property of binding at least 80% of an equal weight of glycocholic acid *in vitro* into a form incapable of dialysis through a cellulose membrane; together with a liquid orally ingestible carrier containing a flavouring or sweetening agent or a solid orally ingestible diluent, the diluent or carrier being compatible with the polymer.

The difference between the required glycocholic acid binding power of the water-insoluble and the water-soluble resins is due to the difference in reactive contact inherent in the nature of these materials. Thus a water-soluble resin in solution is in quite intimate contact with the glycocholic acid and it should therefore bind at least 80% of an equal weight of said acid almost immediately. A water-insoluble resin, because of the heterogeneous system in which it is operating, must be capable of rapidly binding a certain amount of the bile acid and for it the requirement is that at least 30% of an equal weight of said acid be bound within 5 minutes.

In the specification and claims, the term "ionizable amino group as herein defined" means an amino group that will form a substituted ammonium salt on action with an acid, or such groups in the form of acid-

addition or quaternary ammonium salts.

Ability to immobilize glycocholic acid in aqueous solutions *in vitro* is an essential characteristic of the polymers used in the present invention. All polymers which have been found effective *in vivo* for reducing blood cholesterol are capable of immobilizing glycocholic acid. Conversely, the polymers which have been found effective in immobilizing glycocholic acid in aqueous solutions *in vitro* are also effective cholesterol blood level reducing agents *in vivo*. Polymers which do not immobilize glycocholic acid in aqueous solution are ineffective in cholesterol blood level reduction.

Glycocholic acid is immobilized either by removal as a precipitate or by sequestration in solution. The effective insoluble anion-exchange resins immobilize glycocholic acid by removal as a precipitate, presumably the glycocholate form of the resin. Effective water-soluble polymers generally function by sequestering glycocholic acid in a soluble complex.

The surprising correlation between glycocholic acid-binding power and the ability to reduce cholesterol blood levels in man and other animals apparently can be explained by the fact that the system maintains a substantially constant bile acid level in spite of the administration of a material which effectively removes bile acids from the system. Administration of a composition of this invention probably reduces bile acid level *in vivo* in a manner similar to the sequestration of bile acids *in vitro*. Cholesterol is oxidized to cholic acid in the system as bile acids are removed, so as to maintain a substantially constant bile acid level. This of course reduces the cholesterol blood level. This is considered the most probable explanation of the action of the polymers used in the compositions of this invention, although we do not wish to be bound by any theory by way of explanation.

Polymers having a molecular weight of about 3000 or higher are preferred for use as cholesterol blood level reducing agents in compositions according to the present invention. These materials are not absorbed in the alimentary tract and therefore do not cause toxic effects.

One class of effective polymers are those sold under the Trade Mark "Dowex 1". They are polystyrene quarternary ammonium salt resins cross-linked with varying percentages of divinyl benzene, and are useful in the form of a non-toxic salt, such as the chloride, sulphate, acetate, or phosphate, or in the free base form. Any such resins containing 5% or less of divinyl benzene, for example "Dowex 1 × 1", "Dowex 1 × 2", and "Dowex 1 × 4", which contain 1%, 2% and 4% respectively of divinyl benzene, are useful. The efficacy in cholesterol blood level reduction decreases as the percentage of cross-linking agent increases. Cross-linkage in excess of about 5% seriously impairs the efficacy of these resins. Other insoluble amine salt type resins which are cross-linked to only about 5% are also useful in cholesterol blood level reduction.

Various water-soluble non-cross-linked polymers have also been found useful in compositions of the present invention, for instance that sold under the Trade Marks "Acryloid CQ" and Acrysol CQ", a linear acrylic type quaternary ammonium salt polymer having a molecular weight of the order of about 2,000,000. This polymer is soluble in water, and the 5% aqueous solution has a viscosity of 2,500 to 5,000 centipoises at room temperature. The polymer is available from the manufacturer in an aqueous solution containing about 12 to 14% by weight of polymer.

Another polymer which is effective in compositions of the present invention is "Acrysol CA", soluble tertiary amine salts. Apart from the fact that this polymer is a tertiary amine salt rather than a quaternary ammonium salt, its properties in general are the same as those of "Acrysol CQ".

A third water-soluble polymer which has been found quite effective in compositions of this invention is polyethyleneimine, which has the structure

$$(—CH_2CH_2NHCH_2CH_2NH—)_n$$

and an average molecular weight of about 30,000.

Another water-soluble polymer useful in cholesterol blood level reduction is a copolymer of acrylamide and vinyl benzyl trimethylammonium chloride in a weight ratio of about 30:70, having an equivalent weight of about 302 and an average molecular weight of above 100,000.

The minimum effective daily dosage of the useful polymers is about 0.5 g./day in man. Because of the low toxicities of the useful polymers, extremely high dosages can be given without ill effect. From the standpoint of cholesterol serum level reduction, no advantages accrue in increasing the daily dosage above 250 g. Preferred dosages lie in the range of about one to 100 g./day.

Conventional pharmaceutical formulations of resins according to the present invention can be made. In all these formulations it is desirable that the resin, if insoluble, be of a fine particle size, preferably 200 to 400 U.S. Standard mesh. The usual pharmaceutical formulations, such as tablets, elixirs, syrups, aqueous solutions or suspensions with added flavouring, or suspensions in corn oil, are suitable. The unit dosage is of a convenient size, as for example tablets containing from 100 mg. to one gram of the resin, or suspensions of the types just mentioned

containing from about 100 mg. to one gram of polymer in about 5 ml. (one teaspoonful). Examples of various pharmaceutical formulations are as follows:

FORMULATION 1

Capsules containing a mix of the following ingredients are prepared:

"Dowex 1 × 2", anhydrous	500.0 mg.
Magnesium stearate	5.0 mg.
	505.0 mg.

The resin is mixed with magnesium stearate which serves as a lubricant, and the mixture is filled into No. 0 gelatin capsules.

FORMULATION 2

A suspension for oral administration is prepared with the following composition:

"Dowex 1 × 2" aqueous suspension (25% solids)		40.0 g.
Tragacanth		0.27 g.
Sweetening agent (10 parts sodium cyclamate plus one part sodium saccharin)		0.9 cc.
Glycerin U.S.P.		3.6 g.
Water	q.s.	90.0 ml.

The glycerin and tragacanth are mixed and added to 45 ml. of water. The mixture is agitated until homogeneous and heated to about 50°C. The resin is added, followed by the sweetening agent and water to bring the total volume of the suspension to 90 ml. The suspension is agitated and milled.

The sweetening agent specified in this formulation is used in all formulations in this application where a sweetening agent is specified.

Formulations of water-soluble resins may also be prepared according to this invention. Among such formulations are the following:

FORMULATION 3

An aqueous 5% solution of "Acrysol CQ" is made as follows:

"Acrysol CQ" (12.5% w/v aqueous solution)		40 ml.
Sweetening agent		1 ml.
Water	q.s.	100 ml.

The "Acrysol CQ" solution is mixed with the sweetening agent. This mixture is then diluted with water to 100 ml.

FORMULATION 4

An aqueous 5% solution of polyethyleneimine is made as follows:

Polyethyleneimine (50% w/v aqueous solution)		10 ml.
Sweetening agent		1 ml.
Water	q.s.	100 ml.

Conventional preservatives, flavouring agents, and colouring matter may be added, if desired, to any of the above formulations.

FORMULATION 5

The following is an example of a zero calorie oral composition for use in treating pruritis:

"Dowex 1 × 2" resin	10.0 g.
High molecular weight carboxyl-vinyl polymer	0.42 g.
Sodium alignate	0.30 g.
Glucose	0.78 g.
Artificial flavouring	.003 cc.
Alcohol as needed	—
Total	12.0 g.

The flavouring is dissolved in alcohol and added to the glucose, the container being rinsed with more alcohol as needed. The resin, carboxyvinyl polymer, and sodium alginate are mixed and the flavoured glucose is added. The mixture is then comminuted, air dried, and stored in airtight packets of 4.0 g. each.

Resins and polymers which are effective in reducing blood cholesterol concentration are also found to remove glycocholic acid from aqueous solutions. Experiments 1 and 2 illustrate the removal of glycocholic acid from aqueous solution by solid resins and liquid polymers respectively.

EXPERIMENT 1

An aqueous solution containing 10g./litre of sodium glycocholate was prepared and divided into 25-ml. aliquot portions. This solution was assayed according to the following procedure: An aliquot portion of the solution was diluted to obtain an aliquot estimated to contain 0.1 mg. of glycocholic acid in one ml. To this diluted aliquot portion was added 4 ml. of reagent sulphuric acid prepared by diluting 42 ml. of concentrated sulphuric acid with 24 ml. of water. The resulting solution was mixed thoroughly and heated for 15 minutes at 56°C. in a constant temperature bath. After cooling to room temperature, the optical density was determined at 318 mμ using the sulphuric acid reagent blank. The optical density of the original solution was obtained by multiplying the optical density of the diluted aliquot portion by the volume ratio of diluted aliquot to original solution.

Into two 25-ml. aliquot portion of sodium glycocholate solution were introduced 250 mg. of "Dowex 1 × 2" and "Dowex 1 × 4" respectively. This represented a resin weight equal to the weight of sodium glycocholate in solution. The resin was allowed to stand

in the solution for four hours. At the end of this time the optical density of each aliquot portion was measured as described above.

The optical densities of the solutions before and after resin treatment are summarized in Table 1:

TABLE 1

Resin	Original Optical Density	Final Optical Density	Per Cent Removal
"Dowex 1 × 2"	27.00	0.545	98%
"Dowex 1 × 4"	27.00	0.925	96.5%

Since the optical density of sodium glycocholate solutions is directly proportional to the concentration, the percentage removal of sodium glycocholate can be calculated from the original and final optical densities. As shown in Table 1 "Dowex 1 × 2" removed 98% of the sodium glycocholate from the solution and "Dowex 1 × 4" removed 96.5% of the sodium glycocholate. The percentage removal of sodium glycocholate is an approximate indication of the effectiveness of the resin *in vivo*, showing that "Dowex 1 × 2" is somewhat more effective than the more highly cross-linked "Dowex 1 × 4". This was confirmed in *in vivo* tests.

EXPERIMENT 2

A dilute aqueous solution of sodium glycocholate, having a concentration of approximately one g./litre was prepared. Into 25-ml. aliquots of these solutions were introduced "Dowex 1 × 2" and "Dowex 1 × 4", respectively, in amounts equal to ten times the weight of sodium glycocholate in solution. The resins were allowed to stand in the solutions for four hours, at which time the optical densities of the solutions were determined. Results are summarized in Table 2.

TABLE 2

Resin	Original Concentration	Original Optical Density	Final Optical Density	Per Cent Removal
"Dowex 1 × 2"	—	2.50	0.030	98.8%
"Dowex 1 × 4"	—	2.80	0.100	96.4%

EXPERIMENT 3

62.5 mg. of sodium glycocholate and 62.5 mg. of "Acrysol CQ" in 50 ml. of water were placed inside a dialysis bag of the cellulose sheeting sold under the trade mark "Cellophane". The bag was a tubular bag, 30 mm. in diameter, closed at the ends. The bag was placed in a beaker of water containing a volume equal to that inside the bag. The beaker and dialysis bag were allowed to stand for 48 hours, and the solutions inside and outside the bag were analysed for glycocholic acid content by measurment of optical density. The procedure was the same as in Experiment 1. The results are summarized in Table 3.

TABLE 3

Optical Densities

Inside Bag		Outside Bag	
Original	Final	Original	Final
3.150	2.650	0	0.500

The effect of various resins on reducing the blood level of cholesterol was tested *in vivo*. The results are given in Experiments 4 to 8.

EXPERIMENT 4

Male Kerr white leghorn chickens, all 9 weeks old, and weighing between 800 g. and 1,000 g., with an average weight of about 900 g., were divided into two groups of 10 birds each. Two groups served as test groups, and two other groups were used as control groups. All four groups received atherogenic

diet having the following composition in percentage by weight:

Yellow corn meal	46.3%
Soybean meal	30.0%
Fish meal	10.0%
Cottonseed oil	5.0%
Cholesterol	2.0%
Alfalfa meal	2.0%
Steamed bone meal	2.0%
Ground limestone	1.5%
Sodium chloride	0.5%
Choline chloride	0.1%
Manganese sulphate	0.02%
Inositol	0.05%
Vitamin supplements* and inerts	Balance

*The vitamin supplements included the following in the amounts indicated per 100 g. of feed:

p-Aminobenzoic acid	15.0 mg.
Niacin	2.0 mg.
Calcium pantothenate	1.5 mg.
Pyridoxine	0.5 mg.
Riboflavin	0.5 mg.
Thiamine	0.25 mg.
Vitamin A	4000 units
Vitamin D	750 units
Menadione	50 mcg.
Biotin	12.5 mcg.
Vitamin B_{12}	5.0 mcg.

The average consumption of diet was about 80 g. per bird per day.

The two test groups received, in addition to the atherogenic diet, one per cent by weight (based on the weight of diet) of "Dowex 1 × 1" and Dowex 1 × 2", respectively, in the chloride form. This amount to about 800 mg. per bird per day based on an average feed consumption of 80 g. per bird per day. After four days the blood plasma cholesterol levels of the four groups were found to be as follows:

TEST GROUP 1	
("Dowex 1 × 1")	77 mg./100 cc.
TEST GROUP 2	
("Dowex 1 × 2")	118 mg./100 cc.
Control group A	286 mg./100 cc.
Control group B	269 mg./100 cc.

EXPERIMENT 5

Three groups of 9-week old, white, male Kerr leghorn chicks, consisting of 10 birds per group, received an atherogenic diet of the composition described in Experiment 1 for four days. The test group also received 1% by weight (based on the weight of diet) of "Acrysol CQ" in the chloride form mixed with the diet. The other two groups served as controls. Blood plasma cholesterol concentrations at the end of four tests were found to be as follows:

TEST GROUP 3	
("Acrysol CQ")	193 mg./100 cc.
Control group C	324 mg./100 cc.
Control group D	270 mg./100 cc.

EXPERIMENT 6

The procedure of Experiment 5 was repeated except that "Separan C" (1% by weight based on the weight of diet) was administered to the test group. Blood plasma cholesterol concentrations were as follows:

TEST GROUP 4	
("Separan C")	180 mg./100 cc.
Control group E	249 mg./100 cc.
Control group F	244 mg./100 cc.

EXPERIMENT 7

White, male Kerr leghorn chickens, all 9-weeks old and divided into groups of ten birds each, were given a basal diet having the following composition:

Yellow corn meal	53.3%
Soybean meal	30.0%
Fish meal	10.0%
Alfalfa meal	2.0%
Steamed bone meal	2.0%
Ground limestone	1.5%
Sodium chloride	0.5%
Choline chloride dry mix (25% choline chloride)	0.4%
Manganese sulphate	0.02%
Inositol	0.05%
Vitamin supplements* and inerts	0.2%

*Same as in atherogenic diet in Experiment 1.

It will be noted that the composition of the basal diet is the same as that of the atherogenic diet except for the replacement of cottonseed oil and cholesterol with cornmeal.

Two test groups received in addition to the basal diet 1%, by weight, of "Dowex 1 × 2" and "Acrysol CQ" respectively. Two additional groups served as controls. The blood plasma cholesterol concentrations of the two test groups and the two control groups after four days were found to be as follows:

TEST GROUP 5	
("Dowex 1 × 2")	60 mg./100 cc.
TEST GROUP 6	
("Acrysol CQ")	61 mg./100 cc.
Control group G	79 mg./100 cc.
Control group H	74 mg./100 cc.

EXPERIMENT 8

The procedure of Experiment 7 was repeated except that the two test groups received 1% by weight (based on the weight of diet of "Acrysol CA" and polyethyleneimine, respectively. Blood plasma cholesterol levels after four days were found to be as follows:

TEST GROUP 7	
("Acrysol CA")	64. mg./100 cc.
TEST GROUP 8	
(polyethyleneimine)	63 mg./100 cc.
Control group I	76 mg./100 cc.
Control group J	69 mg./100 cc.

EXPERIMENT 9

Two groups of 9-week old, white, male Kerr leghorn chickens, consisting of ten birds in each group, received the atherogenic diet described in Experiment 1. These birds received, admixed with diet, 1% dry weight of "Dowex 1 × 2" hydroxyl form. A control group of 98 birds received the same atherogenic diet without the "Dowex 1 × 2". Blood plasma cholesterol determinations were made at the end of four days. The blood plasma cholesterol concentrations, in mg. per 100 cc. (mg. %), were as follows:

Test group 9 ("Dowex 1 × 2")	118 mg./100 cc.
Test group 10 ("Dowex 1 × 2")	176 mg./100 cc.
Average of test groups 9 and 10	147 mg./100 cc.
Control group K (98 birds)	284 mg./100 cc.

The foregoing examples illustrate the substantial reduction of blood cholesterol level in chickens which is achieved by the administration of a glycocholic acid-binding polymer according to this invention. Similar results are attained in dogs as shown by the experiments which follow.

EXPERIMENT 10

The effect of "Dowex 1 × 2" on the blood plasma cholesterol level of a dog was studied in a test in which the dog was observed first as a control and then as a test animal. During the control period, which lasted 51 days, the dog was given a commercial canine diet with no supplements. A 70-day test period followed, during which the dog received "Dowex 1 × 2" in addition to the basal diet received during the control period. The "Dowex 1 × 2" was admixed with the diet. The dog received 25 g. of "Dowex 1 × 2" on the first day of the test period, 50 g. on the second day, 75 g. on the third day, and 100 g. on the fourth and each succeeding day, except the fifth and sixth days when the dog fasted.

During the control period the blood plasma cholesterol fluctuated between 94 mg./100 cc. and 110 mg./100 cc., and the body weight declined from 18.4 kg. to 17.7 kg. During the test period, the blood plasma cholesterol level fell steadily from 104 mg./100 cc. to 73 mg./100 cc., showing that "Dowex 1 × 2" is effective in lowering blood cholesterol levels. Results are summarised in the following table.

	Blood Plasma Cholesterol, mg. %	Body Weight, Kg.
Control Period:		
Day 1	110	18.4
Day 11	94	18.3
Day 22	107	18.0
Day 25	95	17.9
Day 39	108	17.6
Day 51	103	17.7
Test Period:		
Day 1	104	17.7
Day 3	91	—
Day 8	79	17.8 (est.)
Day 35	75	16.7
Day 70	73	17.6

EXPERIMENT 11

An 83-day test on four dogs was carried out to determine the effectiveness of "Acrysol CQ" in lowering blood cholesterol. Dog 1 served as a control throughout the entire test. The other dogs underwent alternate control and test periods. A commerical canine diet was given to each dog throughout the test. This diet was supplemented with 75 ml. per day of "Acrysol CQ" during test periods.

The test periods of dogs 2, 3 and 4 were as follows: Dog 2, from day 36 to day 83, inclusive; dog 3, from day 6 to day 47, inclusive; dog 4, from day 6 to day 12, inclusive, and from day 26 to day 83, inclusive.

Dog. 3 was sacrificed on day 48. Autopsy revealed no signs of toxicity.

The blood plasma cholesterol levels in mg. per 100 cc. (mg./1%) are given in the table below. In this table test periods for each dog are denoted by an asterisk following the blood cholesterol level; other times are control periods.

PLASMA TOTAL CHOLESTEROL
mg. %

Day	Dog 1	Dog 2	Dog 3	Dog 4
1	96	133	84	79
2	95	127	82	74
5	107	134	83	73
6	100	111	75*	65*
7	103	110	63*	56*
8	91	104	54*	50*
9	113	121	56*	53*
12	98	111	47*	42*
13	103	111	41*	49
14	96	114	36*	43
15	102	119	35*	62
16	98	113	39*	60
19	95	124	43*	69
20	93	119	46*	72
22	97	121	41*	72
23	93	118	41*	71
26	94	115	42*	60*
29	95	117	46*	49*
33	90	109	49*	48*
36	93	63*	49*	51*
37	86	59*	49*	56*
40	95	60*	53*	54*
43	86	74*	49*	54*

* indicates test period.

PLASMA TOTAL CHOLESTEROL
mg. %

Day	Dog 1	Dog 2	Dog 3	Dog 4
47	90	75*	62*	62*
50	98	81*	Sac.	56*
54	89	82*		56*
57	91	76*		54*
61	93	82*		63*
64	95	84*		57*
68	89	83*		63*
71	92	80*		63*
76	86	81*		63*
83	90	88*		61*

* indicates test period.

WHAT WE CLAIM IS:—

1. An orally administerable pharmaceutical composition for binding bile acids in the gastro-intestinal tract into a nonabsorbable form, comprising a synthetic non-toxic polymer having a polymeric skeleton inert to digestive enzymes and a molecular weight in excess of about 3,000 and containing ionizable amino groups as herein defined, the polymer, if water-insoluble, having the property of binding at least 30% of the available glycocholic acid into a form incapable of dialysis through a cellulose membrane within 5 minutes when exposed to an aqueous solution of an equal weight of said acid, and having a moisture content greater than 65% after equilibration with air at 100% relative humidity at 25°C, and, if water-soluble, having an equivalent weight, based on the ionizable amino groups of less than 500 and the property of binding at least 80% of an equal weight of glycocholic acid *in vitro* into a form incapable of dialysis through a cellulose membrane; together with a liquid orally ingestible carrier containing a flavouring or sweetening agent or a solid orally ingestible diluent, the diluent or carrier being compatible with the polymer.

2. A composition as claimed in Claim 1, in which the ionizable amino group is a quarternary amino group.

3. A composition as claimed in Claim 1, in which the ionizable amino group is an amine salt.

4. A composition as claimed in Claim 1, in which the polymer is a polyethylene imine.

5. A composition as claimed in Claim 1, in which the polymer is an acrylic polymer having quarternary ammonium alkyl ester side chains.

6. A composition as claimed in any preceding claim, in which the polymer is not cross-linked.

7. An orally administerable pharmaceutical composition for binding bile acids *in vivo* into a non-absorbable form, substantially as hereinbefore described with reference to any of the foregoing Examples.

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